The potential prognostic and therapeutic application of tissue and circulating microRNAs in cervical cancer

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The potential prognostic and therapeutic application of Tissue and Circulating microRNAs in cervical cancer

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Abstract

Cervical cancer (CC) is a common malignancy in women and a major cause of cancer- related mortality globally. Some novel biomarkers may enable the early diagnosis and monitoring of CC. MicroRNAs are small noncoding RNAs that control gene translation at a post transcriptional level. Hence the deregulation of these molecules can cause many diseases. There appears to be an association between aberrant miRNA expression and CC, but the molecular mechanisms involved in the development of CC remain unknown. The upregulation of some circulating miRNAs, e.g. miRNA-20a, miRNA-203, miRNA-21, miRNA-205, miRNA-218, and miR-485-5, as well as tissue specific-miRNAs, e.g. miR-7, miR-10a, miR-17-5p, miR-135b, miR-149 and miR-203 has been found in patients with CC. There is also growing evidence for the importance of miRNAs in the development of drug-resistance. This review therefore highlights recently published preclinical and clinical investigation performed on tissue-specific and circulating miRNAs, as potential biomarkers for the detection of patients at early stages of CC, in the prediction of prognosis, and monitoring of their response to therapy.

Key word: cervical cancer, CIN, MiRNA, circulating biomarker, tissue-specific biomarker, HPV

Introduction:

Cervical cancer (CC) is the fourth most common cancer in women and a major cause of cancer-related mortality. A comprehensive approach that includes early diagnosis of CC can reduce the high mortality rate of this disease globally (1). Thus the identification of novel prognostic and predictive biomarkers is an important factor in the management of patients during therapy and in the early diagnosis of cervical cancer.

MicroRNAs (miRNAs) are endogenous single-stranded noncoding RNAs that control gene expression at post-transcriptional level by means of miRNA-mRNA interactions. These interactions lead to degradation or inhibition of mRNA translation (2). MicroRNAs are of great importance in all biological processes, thus abnormal expression of these molecules has been found to be associated with several conditions. In 2002 it was first reported that miRNAs are associated with cancer and attention was drawn to these molecules because of their potential value as biomarkers(3). MicroRNAs can circulate in several forms: freely in blood, encapsulated in exosomes or associated with protein complexes. Studies have shown a deregulation of their expression in cervical cancer patients(4). The expression pattern of miRNAs in the tumor tissue of cervical cancer patients also differed from healthy subjects (5). Other studies have evaluated the role of miRNAs as therapeutic targets. This requires further comprehensive studies.

There has been a recent increasing interest in the miRNAs in relation to cancer diagnosis.

Circulating microRNAs in cervical cancer

MiRNAs circulate in the bloodstream, often within micro vesicles or protected by binding proteins in blood. They can be chemically altered (e.g., methylation), making them highly resistant to decay by ribonuclease and may therefore be potential biomarkers due to their stability, and ease of measurement. However, the source and detailed mechanisms of cellular

release of circulating miRNAs remains largely unknown. Studies have shown that miRNAs can be released into the circulation from cells by apoptotic and necrotic cell death. MiRNAs can also be secreted by cancer cells, and this may enhance tumor growth and spread, and are also released by numerous other cell types such as blood cells, immune effector cells, and other cells involved in tumor attack and inflammatory response. Zhao et al, demonstrated that there are high serum concentrations of miRNA-20a and miRNA-203 in patients with CC compared to healthy subjects (6). Ma and coworkers have reported that miRNA-205 could also be a promising biomarker as its serum levels are increased in patients with cervical cancer (7). MiRNA-21 could play a role in the diagnosis of cervical cancer metastasis. Future studies are needed to explore whether a therapeutic intervention can be developed based on this finding that could be used to block lymph node metastasis in cervical cancer. (8) Yu and collaborators have reported that the expression of miRNA-218 alters according to the different stages of cancer: cancer pathological pattern and lymph node metastasis, and so it has been proposed that miRNA-218 could be used in the cancer staging process (9). This view is partially supported by Nagamitsu et al (2015), who have shown an increased level of serum miRNA-1290 along with the stage of CC. On the other hand, the authors did not observe any significant relationship between miRNA expression level and lymph node metastasis. This research also provides evidence of a much higher level of miR-485-5p, miR-1246, miR-1275 and miR-1290 among cervical cancer patients in comparison with healthy individuals (10).

Exosomes and miRNAs

Exosomes are nano-sized (30–100 nm) membrane extracellular vesicles, that originate from numerous types of cells, including: tumor cells, reticulocytes, neurons, and immune cells in physiological and pathological conditions. Exosomes comprise a lipid bilayer containing

ceramides, phosphoglycerides, cholesterols, and sphingolipids. Since exosomes originate from cells, they contain several cellular component, that include: carbohydrates, lipids, proteins, peptides, DNAs, and RNAs (Figure 1). Exosomes are present in most body fluids, including: saliva, blood, breast milk, and urine. Once released, exosomes bind to other cells via receptor-ligand mechanisms, or deliver intra-exosomal elements without specific binding. Exosomes contain genetic information of their cellular source, and circulate throughout the circulatory system. Therefore, the biomolecules that they contain, such as miRNAs may be potentially useful biomarkers, allowing non-invasive disease diagnosis (2).

Numerous studies have shown that the components secreted by exosomes from cancer cells are associated with tumor promotion and malignancy. According to Liu and colleagues, exosomal levels of miRNA-21 and miRNA-146a were higher in samples from patients with cervical cancer compared to those who were HPV-positive, or HPV-negative normal counterparts. Furthermore, miRNA-21 and miRNA-146a were expressed at a higher levels in exosomes from HPV-positive patients than in HPV-negative subjects.(11) Similarly, as noted by Honegger et al, expression of E6/E7 oncogenes in HPV-positive cancer cells could affect the exosomal expression level of 7 cervical cancer-associated miRNAs, with a down-regulation of let-7d-5p, miR-20a-5p, miR-378a-3p, miR-423-3p, miR-7-5p, and miR-92a-3p and up-regulation of miR-21-5p (12). A recent review concluded that miRNA-7, miRNA-99, miRNA-378 and the miRNA 17-92 families of miRNAs are the major exosomal miRNAs that are altered in HPV associated cancers, particularly CC (13).

Tissue specific MiRNAs in cervical cancer

Different miRNA families have evolved to provide a diverse range of transcriptional products. Sequence maintenance and RNA binding-proteins have evolved together to gain a final fine-tuning gene adjustment in various cells and tissues Several miRNAs have been identified that

are related to CC growth. For instance, miR-7, miR-10a, miR-17-5p, miR-19a and miR-19b, miR-21, miR-125b and miR-138, each regulates tumorigenic, or tumor suppressor factors: XIAP, CHL1, TP53INP1, CUL5, PDCD4, PIK3CD, and hTERT respectively. These factors are negatively regulated by the above miRNAs apart from CUL5. (14) Furthermore, Li et al have suggested that miRNA-100 is expressed at higher levels in low-grade CIN samples compared to high-grade CIN . MiRNA-100 is a negative regulator of PLK1, whose overexpression is often observed in tumor cells. Therefore, the adverse impact of miRNA-100 on cell growth would be justifiable. (15) In an investigation into cervical cancer-associated miRNAs, Pereira et al found that miR-21, miR-135b, miR-223, miR-301b and miR-135b are over-expressed miRNAs, that could be useful to diagnose cervical cancer (16). Lee et al has suggested that miR-199-s, miR-9, miR199a, miR-199a, miR-199b, miR-145, miR-133a, miR-133b, miR-214 and miR-127 are the most significantly up-regulated miRNAs and miR-149 and miR-203 as two down-regulated miRNAs in tumor samples. In order to understand the effect of miRNA-199a expression level on cell growth, Lee et al transfected anti-miRNA-199a into the SiHa and ME-180 tumour cell lines, and observed a significant reduction in miRNA-199a expression levels, suggesting a cancer growth blocker function of anti-miRNA-199a. (17) Reshmi et al have noted that some miRNAs (miR-126, miR-143, miR-145, miR-218, and miR-424) are downregulated and others upregulated (miR-15b, miR-16, miR-146a, miR-155, and miR-223) in CC tissues. They also proposed that different miRNA species could have a tumor suppressive or oncogenic function in CC tissues. (18) For instance, it has been shown that miRNA-143 and miRNA-145 act as a suppressive factor for tumor progression, whereas overexpression of miRNA-146a has a tumorogenic effect and reduce cervical cancer cell doubling time (19). Granados-López conclude that miR-10a-5p and miR-10b-5p play an adverse role in cervical cancer development. MiR-10a-5p behaves as an oncogene and its expression level increases from stage 1 to stage 4 of cervical cancer. Whereas, miR-10b-5p has

a tumor-suppressor function as a result of its ability to down-regulate Homeobox A1 (HOXA1). (20) A further opposing function in one family of miRNAs has been reported between miR-15a-3p and miR-15a-5p (21). In addition, miR-15 and miR-16 have been placed in the group of cancer growth blocker miRNAs, as their overexpression could affect negatively on HeLa cells' G1-S cycle (21). A recent study by Lopez et al demonstrated that miRNA-1-3p is an anti-oncomiRNA; as it regulates glucose-6-phosphate dehydrogenase (G6PD) level, it contributes to programmed cell death and a reduction in cancer growth (22).

MiRNAs as Therapeutic Targets

Many clinical trials have investigated the relationship between miRNA and different disease such as malignances, asthma, psychotic depression, Irritable bowel syndrome, diabetes mellitus, and cardiovascular disease (23-27). Several clinical studies are in progress on the effect of miRNA on a variety of cancers like prostate, breast, melanoma, skin, lung cancers, etc (28-32). In relation to these studies, scientists have focused on the use of miRNAs as a diagnostic, predictive, or prognostic biomarkers for cancer treatment. For example, in a recent study, Hagstrom AD and Denham have shown miRNA expression profile is different between high and low responders to resistance training in breast cancer patients (33). In the first-in-man, phase 1, open-label, dose-escalation study, scientists examine the Safety and activity of microRNA-loaded minicells in patients with recurrent malignant pleural mesothelioma. They could find The acceptable safety profile and early signs of activity of TargomiRs in patients with malignant pleural mesothelioma (34) in the first-in-human, phase I study, which assessed the maximum tolerated dose (MTD), safety, pharmacokinetics, and clinical activity of MRX34, a liposomal miR-34a, in patients with advanced solid tumors, results have been shown, MRX34 treatment with dexamethasone premedication was associated with acceptable safety and showed evidence of proloferation activity in a subset of patients with advanced solid tumors (35).

. In CC, the most common treatments are surgery, radiotherapy, chemotherapy (36). Mou et al have reported that miR-148b is a tumor suppressor of CC, that works by inducing G1/S-phase cell cycle arrest and apoptosis in a caspase-3-dependent manner. Hence, overexpression of miR-148b may be a new therapeutic approach for CC (37). Wand and colleagues have found that miR-214 is frequently downregulated in tumor tissues chiefly in CIN III. MiR-214 can prevent cell migration and invasion and enhanced drug sensitivity in cervical cancer cells (36). Zhou et al have shown that miR-138 expression is downregulated in cervical cancer and is negatively associated with advanced FIGO (International Federation of Gynecology and Obstetrics) stage and lymph node metastasis. In other words, miR-138 functions as a tumor suppressor in cervical cancer by suppressing cancer growth, preventing cell migration and increasing apoptosis (38). Another study has shown that miR-195 inhibits CC cell proliferation, invasion and migration (39). Therefore miR-195 may be a potential target for the treatment of CC (39). Su and colleagues have reported that patients with cervical cancer, who have a decreased expression of miR-34a and miR-206, have an increased risk of lymph node metastasis, advanced stage and histological grade and shorter survival in the study (40). MicroRNA 21 is recognized as the direct target gene of GAS5 and over expression of GAS5 prevents cervical cancer cell growth, invasion and migration according to Wen et al (41). Li and colleagues have shown that miR-138 is a potential prognostic biomarker and miR-138 functions as tumor suppressor in CC (42). Li et al have reported that miR-378 is a novel therapeutic strategy in CC (43). MiR-30e can suppress the proliferation and invasion of CC cells through targeting mRNA and it can be a new therapeutic target for CC in the future (44). Wang et al have shown that overexpression of miR-34a-5p prevented proliferation of CC cells and promoted apoptosis of these cells by down-regulating Bcl-2 expression (45). Another study found that miR-187 inhibited the proliferation and promoted apoptosis of cervical cancer cells and it also inhibited the growth of CC cells in nude mice in an in vivo experiment (46).

Conclusion:

CC is a major cause of cancer-related mortality in women. Thus identification of novel prognostic and predictive biomarkers is essential in management of patients during the therapy and early diagnosis of cancer. Numerous recent studies have highlighted the predictive and therapeutic role of miRNAs in cervical cancer. However, there is a need for more comprehensive studies to light up the clinical utility of these biomarkers.

Many studies have evaluated different types of circulating or tissue specific miRNAs and their role in diagnosis of cervical cancer. The expression level of some of these differs significantly in CC patients from healthy individuals, and thus they can be used as biomarkers to diagnose cancer in early stages. Many studies support the therapeutic potential of miRNAs in cervical cancer. MicroRNAs can suppress the proliferation and invasion of cancer cells and as a result prevent metastasis. It is also stated that these markers can induce apoptosis of the cancer cells. On the other hand, some miRNAs are oncogenes and increase simultaneously with the stages of cancer. The studies of microRNAs are very promising and future studies will simplify the diagnosis and treatment of cancer. Understanding of molecular pathways of miRNAs that regulate the development of CC can provide an insight into their future clinical application.

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Figure legend

Figure 1. Exosomes and microRNAs. Exosomes contain genetic information of their cellular source, and circulate throughout body, indictaing its values as non-invasive biomarkers